DR. PAUL MACDARAGH RYAN (Orcid ID : 0000-0001-7251-6725)

Article type : Review

Is Adipose Tissue a Reservoir for Viral Spread, Immune Activation and Cytokine Amplification in COVID-19

Paul MacDaragh Ryan, Noel M Caplice

Centre for Research in Vascular Biology,
APC Microbiome Ireland,
University College Cork,
Cork University Hospital
Cork, Ireland

Perspective Paper

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/oby.22843

Address for correspondence:
Prof. Noel M Caplice M.D., Ph.D.
Centre for Research in Vascular Biology,
APC Microbiome Ireland
Cork University Hospital,
University College Cork,
Cork, Ireland
Tel: int + 353 871201487
Email: n.caplice@ucc.ie

Funding: No extramural funding was sought for this manuscript.

Conflict of Interest: Dr. Ryan and Prof. Caplice have nothing to disclose.

ABSTRACT

Coronavirus disease 2019 (COVID-19), the worst pandemic in more than a century, has claimed >125,000 lives worldwide to date. Emerging predictors for poor outcome include advanced age, male gender, pre-existing cardiovascular disease and risk factors including hypertension, diabetes and more recently obesity. Herein, we posit new obesity-driven predictors of poor COVID-19 outcome, over and above the more obvious extant risks associated with obesity including cardiometabolic disease and hypoventilation syndrome in intensive care patients. We outline a theoretical mechanistic framework whereby adipose tissue in subjects with obesity may act as a reservoir for more extensive viral spread with increased shedding, immune activation and cytokine amplification. We propose studies to test this reservoir concept with a focus on specific cytokine pathways that might be amplified in subjects with obesity and COVID-19. Finally, we underscore emerging therapeutic strategies that might benefit subsets of patients in which cytokine amplification is excessive and potentially fatal.

Coronavirus disease 2019 (COVID-19) has now infected over 2 million people worldwide, with a death toll of more than 125,000 people. Emerging risk factors for poor outcome in this disease include age, male gender, cardiovascular co-morbidities including hypertension, prior cardiovascular disease, diabetes and more recently obesity (1). The Center for Disease Control and Prevention (CDC, Atlanta, USA) has now reported a 3-fold increase in death in New Orleans compared to New York and speculation has grown as to whether these worrying mortality statistics might in part be attributable to higher levels of morbid obesity (2). In this perspective paper we develop a theoretical framework that describes why subjects with obesity may be at increased risk of poor outcomes compared to non-obese counterparts (3). We propose a mechanism for adverse consequences of virus seeding to adipose tissue (AT) with potential for prolonged viral shedding and extended cytokine activation in a voluminous and richly vascularized organ that is already perturbed in a metabolic and inflammatory sense in human subjects with obesity (4). We present a rationale for testing this concept in COVID-19 patients through prospective studies of subjects with and without obesity with accessible adipose tissue and plasma to determine whether or not an inflammatory and cytokine signature presages a systemic cytokine storm and clinical decline.

Evidence for association of obesity with worse COVID-19 outcome

Obesity was not specifically reported in the initial cohort studies of COVID-19 from Wuhan, China (5) but regional epidemiological data from the USA suggests that at least 25% of patients who die of this disease have obesity, which is similar to reported rates of cardiovascular disease in the same high risk group (21%) (6). More recently, a small retrospective study of 85 subjects with COVID-19 identified obesity as a risk factor for admission to ICU with patients requiring increased medical attention (3). Moreover, in the influenza A subtype H1N1 pandemic, obesity was also strongly associated with a worse disease outcome and death (7). Together these data raise the question of whether there is a mechanistic link between obesity and disease survival, and whether obesity over and above its endocrine or cardiometabolic associations might independently contribute to COVID-19 risk.

Likely mechanisms involved in poor outcomes in subjects with obesity

It is clear that obesity could contribute to both diabetic and cardiovascular risk of COVID-19 and these elements of risk, in addition to more recently thrombosis, have been well described in the scientific literature (8, 9, 10, 11, 12). Moreover, obesity is an independent risk for hypoventilation syndrome in ICU patients (13) and, thus, could contribute to respiratory failure in

patients with acute respiratory distress syndrome (ARDS) (14). Here, we propose additional unheralded pathophysiologic aspects of increased AT burden in morbid obesity that may amplify the pro-inflammatory response to extensive viral infection. AT should be viewed as a highly active organ interfacing immune, endocrine and metabolic homeostasis throughout the body (15). In subjects with obesity there is marked dysregulation of myeloid and lymphoid responses within AT with associated dysregulation of cytokine profiles (15). Intrinsically bound to this are endocrine and metabolic derangements including insulin resistance, and adipokine dysregulation with dysfunctional lipid and fatty acid metabolism (16). In highly vascularized adipose tissue, endothelial and smooth muscle cells as well as resident macrophages exhibit additional perturbations in response to an activated renin angiotensin system (RAS) at a local level with attendant depletion and dysfunction of the counter-regulatory angiotensin converting enzyme 2 (ACE2) Mas receptor system (17, 18). This makes AT, particularly in visceral distributions, pro-immunogenic, metabolically active and highly integrated into the cardiovascular system, with the capability to drive acute disease through augmented inflammation at an organ level in the heart, vasculature, pancreas, liver and kidneys (19). This “pre-activation state” of AT in obesity makes this organ a potential target for further immune amplification by external pathogens such as viruses.

Viral spread to AT and potential for activation of resident inflammation and cytokine pathways

Currently there is no evidence for direct SARS-CoV-2 infection of AT, although ACE2 receptor expression represents a basis for viral tropism in several cells within this tissue (20) including adipocytes, smooth muscle cells and endothelial cells (21). Moreover, many AT-resident cells are proven targets for multiple viruses including adipocytes (H1N1, Type A influenza and adenovirus 36 (7, 22, 23)), adipo-stromal cells (Adenovirus 36 (24), CMV (25)), endothelial cells (SARS-CoV (26)), macrophages (influenza A, SARS-CoV, adenovirus36, HIV (26, 27)) and lymphocytes (SARS-CoV, HIV (25, 26)). Although SARS-CoV-2 was detected only at low levels in blood in a small human study (28), we cannot exclude hematogenous spread to AT given very high virus affinity for its target cell receptor. Alternative routes of SARS-CoV-2 spread to AT include local egress of virus, from organs known to be infected, to adjacent visceral fat deposits such as intrathoracic fat (lungs), epicardial fat (heart), peri-renal fat (kidneys) and mesenteric fat (intestines). Finally, shared viral tropism for lung epithelium and adipose tissue has already been shown for H5N1 virus infection (29) and AT significantly prolongs the duration of viral shedding in humans with obesity infected with influenza (22). Were similar tropism of SARS-CoV-2 to occur

within AT of COVID-19 subjects with obesity there exists the potential for prolonged viral shedding in this organ with extended activation of local “pre-activated” immune systems and resident cytokine signalling pathways.

Resident myeloid and lymphoid cells are plentiful in AT and obesity is associated with macrophage (30) and lymphocyte dysfunction (31). Expansion of distinct memory T lymphocytes within AT can also activate aberrant immune responses with wider tissue damage on viral challenge (31). A recent report from Wuhan suggests that SARS-CoV-2 induces a dysregulated immune response in severely ill COVID-19 subjects (32), characterised by reduced numbers of circulating memory T lymphocytes, as well as reduced helper / suppressor T cell and T Reg subtypes. It is tempting to speculate whether already dysfunctional immune responses in subjects with obesity may accentuate this SARS-CoV-2 effect on T cell function.

Specific inflammatory cytokine programmes such TNFα, IL1 and IL6 are known to be pre-activated in AT in the context of obesity (33) and, thus, viral infection may similarly amplify the already primed organ cytokine response in AT. The cytokine storm identified in multiple respiratory viral infections including COVID-19 exhibits diverse interferon, interleukin, chemokine, tumor necrosis factor and colony stimulating factor responses which are beyond the scope of this perspective, but comprehensively reviewed elsewhere (34). The intensity of inflammatory lung responses reflect the imbalance between proinflammatory cytokines (such as TNF and Il1β) and their soluble cognate receptors that inhibit cytokine effects in aqueous phase (35). IL10 produced by macrophages and T lymphocytes (Th2 and T regs) acts as a negative regulator of inflammation; whereas IL6 and its soluble receptor enhance activity of IL6 on target cells providing a mechanism for enhancement of TNF and IL-1β activity when these soluble cognate receptor are particularly high (35). Thus, a balance between pro- and anti-inflammatory mechanisms is critical in maintaining lung tissue homeostasis. It is conceivable that if one or more of these regulatory elements were absent or dysfunctional then this may contribute to a cytokine storm in the lung or in other tissues such as AT where aberrant cytokine activation exists. Temporal studies of cytokine dynamics in human “cytokine storm” models show IL6 sustains activation of multiple cytokine pathways for many days post initial immune insult (36). Interestingly, in early COVID-19 studies IL6 was a strong independent predictor of mortality (37). Human AT is a major source of IL6 and its receptor IL6R (38) and, thus, AT may provide a reservoir for IL6 activation and cascade signalling in viral infection (Figure). Viral spread from affected organs to adjacent AT may take days, with subsequent prolonged viral shedding

contributing to the delayed cytokine storm and consequences for tissue injury in patients with COVID-19.

Testing AT inflammatory cytokine reservoir concept in COVID-19

Initial studies should aim to detect SARS-CoV-2 in AT upon autopsy of subjects who have died of COVID-19. Focus should be on analysis of specific cells that have evidence of infection by immunocytopathic and in situ viral detection techniques. Parallel studies should identify whether specific cell types in AT can support SARS-CoV-2 infection and replication ex vivo. With respect to cytokine storm, an integrated systems biology approach would enable multiple pathways to be assessed simultaneously. In this regard, cytokine and chemokine genomic data analysis in blood and AT would be an important first step. Moreover a weighted gene correlation network analysis of SARS-CoV-2 mediated transcriptional response in infected cells could also be used as a model for human AT analysis downstream (39). Interesting aspects of transcriptional network analysis could then be tested in appropriate animal models to determine pivotal components of the cytokine storm including key cytokine and chemokine genes that are conserved across species (40). These insights may allow rational diagnostics and therapeutic strategies to be developed. In line with this, IL6 inhibition has already been proposed as a treatment in COVID-19 and the results of trials of Tocilizumab are awaited (41). It would be interesting to examine whether subjects with obesity, who are expected to have higher circulating IL6 levels compared to lean counterparts, respond more favourably to IL6 inhibition strategies in COVID-19 in a post hoc analysis of this RCT. Similarly, tissue and systemic analysis of cytokine dynamics may identify likely responders and non-responders to such therapy.

In summary we present a rationale for studying the relationship between obesity and COVID-19 disease severity. We provide a theoretical framework whereby viral systemic spread, entry and prolonged viral shedding in already “inflamed” AT may augment immune responses with consequences for cytokine cascade amplification. We highlight AT as an abundant source for local and systemic enrichment of cytokines, some already independently associated with increased COVID-19 mortality. Finally we suggest a series of research studies to identify whether a mechanistic link exists between AT, SARS-CoV-2 infection, organ seeding of infection, immune activation and the delayed cytokine storm known to presage rapid clinical decline in high risk COVID-19 patients.

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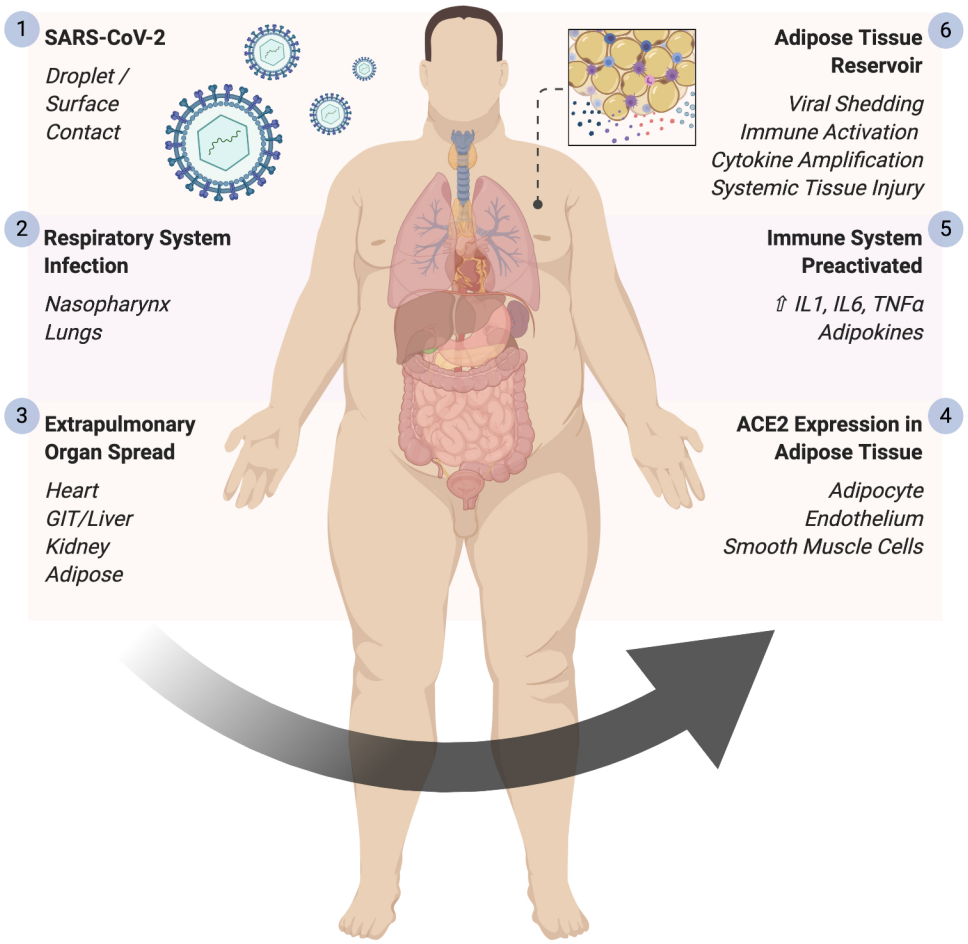
FIGURE LEGEND

Figure. Adipose Tissue as a Reservoir for SARS-CoV-2 Spread, Viral Shedding, Immune Activation and Cytokine Amplification. Schematic demonstrating the proposed centrality of adipose tissue in the dissemination of SARS-CoV-2 and the ensuing systemic immune activation. Created with Biorender.com.



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